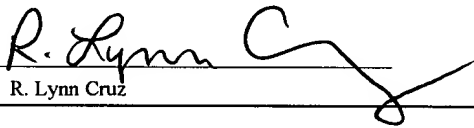


CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand filed with the United States Patent and Trademark Office in Washington, D.C. on November 12, 1999.


R. Lynn Cruz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

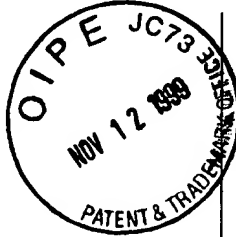
In the application of:

Irving BOIME et al.

Serial No.: 08/918,288

Filing Date: 25 August 1997

For: SINGLE-CHAIN FORMS OF THE
GLYCOPROTEIN HORMONE
QUARTET



Examiner: L. Spector

Group Art Unit: 1646

DECLARATION OF ELLIOT L. ELSON
PURSUANT TO 37 C.F.R § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Elliot L. Elson, declare as follows:

1. I am professor of Biochemistry and Molecular Biophysics at Washington University. I am a practitioner in the field of protein chemistry and protein physical characteristics. A copy of a summary of my curriculum vitae is attached as Exhibit A.

2. I understand that an issue has arisen in the above-referenced case relating to the predictability of success in maintaining biological activity when the subunits of a multimeric protein are prepared as a single fusion protein. I understand that the Patent Office has cited the disclosure of a patent to Thomason, U.S. Patent No. 5,705,484, which describes a single-chain form of a protein belonging to the platelet-derived growth factor (PDGF) family. The subunits which make up the PDGF multimers are held together through disulfide bonds. The

glycoprotein hormones which are the subject of the invention in the above-referenced application are, on the other hand, noncovalently associated subunits.

3. Linking together the subunits of any multimer distorts, to a certain extent, the conformation that would have been obtained had the subunits been associated in a normal manner. Thus, it is, as a general matter, impossible to predict that successful results obtained with similar proteins will extrapolate successfully to dissimilar ones. While it is reasonable to conclude that success with one member of a closely related family will also be achieved with three closely related family members, it is entirely unpredictable whether this success would carry over to unrelated proteins.

4. This unpredictability applies even among unrelated multimers which share the property that their subunits are covalently linked by disulfide bonds. The unpredictability is much higher when one attempts to predict, from results for this group, to those obtained when the subunits are noncovalently linked. This is due to the fact that the distortion caused by the construction of the multimer as a single chain is substantially less when the subunits are covalently bonded through disulfides than is the case when they are noncovalently associated. The biological activity is affected by the degree of association of the subunits and the rate of their dissociation. The differences between the native protein and the single-chain forms is much more pronounced in the case of noncovalently associated subunits.

5. Based on the above, I conclude that it cannot be predicted from the apparent success achieved by Thomason with respect to PDGF whether the glycoprotein hormones would or would not maintain their biological activity when prepared in single-chain form.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Executed at St. Louis, Missouri on Oct 28, 1999.

Elliot L. Elson

Elliot L. Elson

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

| | | | | |
|--|--|---|---------|------------------|
| NAME Elliot L. Elson | | POSITION TITLE Professor of Biochemistry & Molecular Biophysics | | |
| EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.) | | | | |
| INSTITUTION AND LOCATION | | DEGREE (if applicable) | YEAR(s) | FIELD OF STUDY |
| Harvard University | | A.B. | 1959 | Biochemical Sci. |
| Stanford University | | Ph.D. | 1966 | Biochemistry |

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1968-1974 Assistant Professor of Chemistry, Cornell University, Ithaca, New York.
 1974-1978 Associate Professor of Chemistry, Cornell University, Ithaca, New York.
 1978-1979 Professor of Chemistry, Cornell University, Ithaca, New York.
 July, 1979- Professor of Biological Chemistry, Washington University
 Present School of Medicine, St. Louis, MO.

Member NIH Study Section BBCA, 1975-1979; CMBD, 1987-1991.

Selected Publications

- H. Qian and E.L. Elson. Characterization of Confocal Laser Based Microscope by Digital Image Analysis, An optical sectioning microscopy approach. In Optical Microscopy for Biology (ed. B. Herman, K. Jacobson) Wiley-Liss, NY pp. 119-130 (1990).
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